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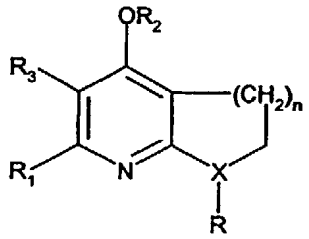
(54) Abstract Title
NOVEL CORTICOTROPIN-RELEASING FACTOR COMPOUNDS

(57) The present invention provides compounds of formula (I)



(I)

wherein

R is aryl or heteroaryl preferably phenyl or pyridine and each of the above groups R may be substituted:

R_1 is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, halogen, NR_4R_5 or cyano;

R_2 corresponds to CHR_7R_8;

R_3 hydrogen, C1-C6 alkyl, halogen;

R_7 is hydrogen, C6-C6 alkenyl or C1-C6 alkyl, and may be substituted by: C1-C6 alkoxy and hydroxy;

R_8 has the same meaning as R_7;

X is carbon or nitrogen; preferably nitrogen.

n is 1 or 2;

with the proviso that 5-(1-ethylpropoxy)-1,2,3,4-tetrahydro-7-methyl-1-(2,4,6-trimethylphenyl)-1,8-naphthyridine is not included. The compounds may be used in the treatment of conditions mediated by corticotropin-releasing factor (CRF). Typically depression, anxiety and irritable or inflammatory bowel disease.

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Chemical Compounds

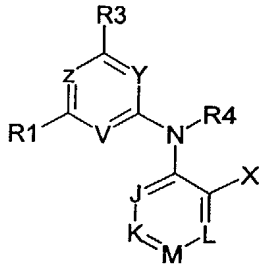
The present invention relates to bicyclic derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in therapy.

The first corticotropin-releasing factor (CRF) was isolated from ovine hypothalami and identified as a 41-amino acid peptide (Vale et al., Science 213: 1394-1397,1981).
CRF has been found to produce profound alterations in endocrine, nervous and immune system function. CRF is believed to be the major physiological regulator of the basal and stress-release of adrenocorticotropic hormone ("ACTH"), Bendorphin, and other pro-opiomelanocortin ("POMC")-derived peptides from the anterior pituitary (Vale et al., Science 213: 1394-1397,1981).

In addition to its role in stimulating the production of ACTH and POMC, CRF appears to be one of the pivotal central nervous system neurotransmitters and plays a crucial role in integrating the body's overall response to stress.
Administration of CRF directly to the brain elicits behavioral, physiological, and endocrine responses identical to those observed for an animal exposed to a stressful environment.
Accordingly, clinical data suggests that CRF receptor antagonists may be useful in the treatment of the neuropsychiatric disorders manifesting hypersecretion of CRF, and, in particular, may represent novel antidepressant and/or anxiolytic drugs.

The first CRF receptor antagonists were peptides (see, e. g., Rivier et al., U. S. Patent No. 4,605,642; Rivier et al., Science 224: 889, 1984). While these peptides established that CRF receptor antagonists can attenuate the pharmacological responses to CRF, peptide CRF receptor antagonists suffer from the usual drawbacks of peptide therapeutics including lack of stability and limited oral activity. More recently, small molecule CRF receptor antagonists have been reported.

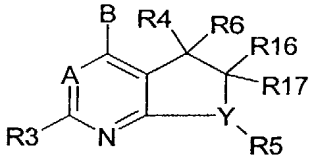
WO 95/10506 describes inter alia compounds of general formula A with general CRF antagonist activity



A

wherein Y may be CR29; V and Z may be nitrogen and carbon, R3 may correspond to an ether derivative and R4 may be taken together with R29 to form a 5-membered ring and is -CH(R28) when R29 is-CH(R30).
There is no disclosure related to compounds corresponding to the above definition.

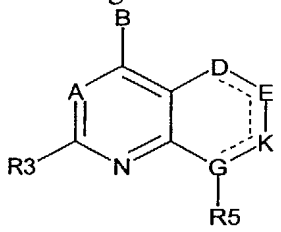
WO 95/33750 also describes compounds of general formula B having CRF antagonistic activity,



B

in which A and Y may be nitrogen and carbon and B may correspond to an ether derivative. There is no disclosure related to compounds corresponding to the above definition.

WO 98/08846 describes compounds of general formula A having CRF antagonistic activity,

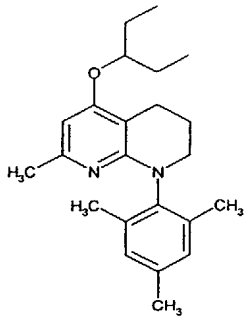


A

wherein A may be carbon, G may be nitrogen, or carbon, B may be an ether derivative and the other groups have the meanings as defined.

There is one compound in which A is carbon, G is nitrogen, B is an ether derivative corresponding to the following structure:

5-(1-ethylpropoxy)-1,2,3,4-tetrahydro-7-methyl-1-(2,4,6-trimethylphenyl)-1,8-naphthyridine



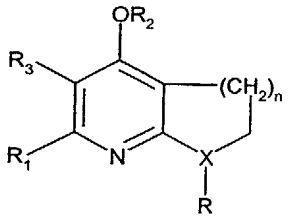
The above compound is disclosed in another patent application, JP 2000038350, useful as antidiabetic.

Due to the physiological significance of CRF, the development of biologically-active small molecules having significant CRF receptor binding activity and which are capable of antagonizing the CRF receptor remains a desirable goal. Such CRF receptor antagonists would be useful in the treatment of endocrine, psychiatric and neurologic conditions or illnesses, including stress-related disorders in general.

While significant strides have been made toward achieving CRF regulation through administration of CRF receptor antagonists, there remains a need in the art for effective small molecule CRF receptor antagonists. There is also a need for pharmaceutical compositions containing such CRF receptor antagonists, as well as methods relating to the use thereof to treat, for example, stress-related disorders. The present invention fulfills these needs, and provides other related advantages.

In particular the invention relates to novel compounds which are potent and specific antagonists of corticotropin-releasing factor (CRF) receptors.

The present invention provides compounds of formula (I) including stereoisomers, prodrugs and pharmaceutically acceptable salts or solvates thereof



(I)

wherein

R	is aryl or heteroaryl and each of the above groups R may be substituted by 1 to 4 groups selected from: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, -COR_4, nitro, -NR_4R_5 cyano, or a group R_6;
R_1	is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, halogen, NR_4R_5 or cyano;
R_2	corresponds to a group CHR_7R_8;
R_3	hydrogen, C1-C6 alkyl, halogen or halo C1-C6 alkyl;
R_4	is hydrogen, C1-C6 alkyl;
R_5	independently from R_4, has the same meanings;
R_6	is C3-C7 cycloalkyl, which may contain one or more double bonds; aryl; or a 5-6 membered heterocycle; wherein each of the above groups R_6 may be substituted by one or more groups selected from: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 mono or dialkylamino, nitro or cyano;
R_7	is hydrogen, C6-C6 alkenyl or C1-C6 alkyl, wherein each of the above groups R_7 may be substituted by one or more groups selected from: C1-C6 alkoxy and hydroxy;
R_8	independently from R_7, has the same meanings;
X	is carbon or nitrogen;
n	is 1 or 2;

with the proviso that 5-(1-ethylpropoxy)-1,2,3,4-tetrahydro-7-methyl-1-(2,4,6-trimethylphenyl)-1,8-naphthyridine is not included

Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, malic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, p-toluensulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric,

gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid (-COOH), esters may be employed, such as methyl esters, ethyl esters, and the like.

With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention.

The term C1-C6 alkyl as used herein as a group or a part of the group refers to a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl.

The term C3-C7 cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; while unsaturated cycloalkyls include cyclopentenyl and cyclohexenyl, and the like.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term halo C1-C6 alkyl means an alkyl group having one or more carbon atoms and wherein at least one hydrogen atom is replaced with halogen such as for example a trifluoromethyl and the like.

The term C2-C6 alkenyl defines straight or branched chain hydrocarbon radicals containing one or more double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl or 3-hexenyl and the like.

The term C1-C6 alkoxy group may be a linear or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy and the like.

The term halo C1-C6 alkoxy group may be a C1-C6 alkoxy group as defined before substituted with at least one halogen, preferably fluorine, such as difluoromethoxy, or trifluoromethoxy.

The term C2-C6 alkynyl defines straight or branched chain hydrocarbon radicals containing one or more triple bond and having from 2 to 6 carbon atoms including acetylenyl, propynyl, 1-butynyl, 1-pentynyl, 3-methyl-1-butynyl and the like.

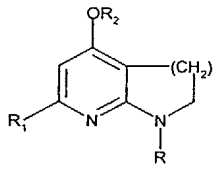
The term aryl means an aromatic carbocyclic moiety such as phenyl, biphenyl or naphthyl.

The term heteroaryl means an aromatic heterocycle ring of 5-to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono-and bicyclic ring systems.

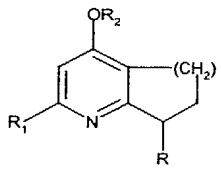
Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, triazolyl, tetrazolyl, and quinazolinyl.

The term 5-6 membered heterocycle means, according to the above definition, a monocyclic heterocyclic ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. The heterocycle may be attached via any heteroatom or carbon atom.Thus, the term include (but are not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

Thus, representative compounds of this invention include the following structure (Ia) and (Ib), depending upon the meaning of X according to the definition of compounds (I) given above, and in which R, R_1 and R_2 are defined as before:

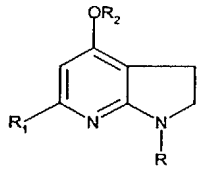


(Ia)

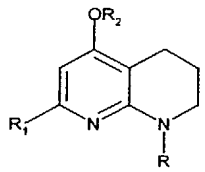


(Ib)

Representative compounds of this invention include the following structure (IIa) and (IIb), depending upon the meaning of n according to the definition of compounds (Ia) given above, and in which R, R_1 and R_2 are defined as before:



(IIa)



(IIb)

Even more preferred embodiments of the invention include, but are not limited to, compounds of the formula (I), (Ia), (Ib), (IIa) and (IIb):
wherein:

- R_1 is C1-C3 alkyl or halo C1-C3 alkyl, preferably methyl or trifluoromethyl;
- R is an aryl group selected from: 2,4-dichlorophenyl, 2-chloro-4-methylphenyl, 2-chloro-4-trifluoromethyl, 2-chloro-4-methoxyphenyl, 2,4-dimethyl-phenyl, 2-methyl-4-methoxyphenyl, 2-methyl-4-chlorophenyl, 2-methyl-4-trifluoromethyl, 2,4-dimethoxyphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-chlorophenyl, 3-methoxy-4-chlorophenyl, 2,5-dimethoxy-4-chlorophenyl, 2-methoxy-4-isopropylphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-isopropylphenyl, 2-methoxy-4-methylphenyl, 2-trifluoromethyl-4-chlorophenyl, 2,4-trifluoromethyl-phenyl, 2-trifluoromethyl-4-methylphenyl, 2-trifluoromethyl-4-methoxyphenyl, 2-bromo-4-isopropylphenyl, 2-methyl-4-cyanophenyl, 2-chloro-4-cyanophenyl, 4-methyl-6-dimethylaminopyridin-3-yl, 4-dimethylamino-6-methyl-pyridin-3-yl, 6-dimethylamino-pyridin-3-yl and 4-dimethylamino-pyridin-3-yl.

Preferred compounds according to the invention are:

1-(2,4-bis-trifluoromethyl-phenyl)-4-(1-ethyl-propoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (1-1);
1-(2,4-dichloro-phenyl)-4-(1-ethyl-propoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine (1-2);
4-[4-(1-ethyl-propoxy)-6-methyl-2,3-dihydro-pyrrolo[2,3-*b*]pyridin-1-yl]3-trifluoromethyl-benzamide (1-3);
4-(1-ethyl-propoxy)-1-[2-(1-ethylpropoxy)-6-trifluoromethyl-pyridin-3-yl]-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-4);

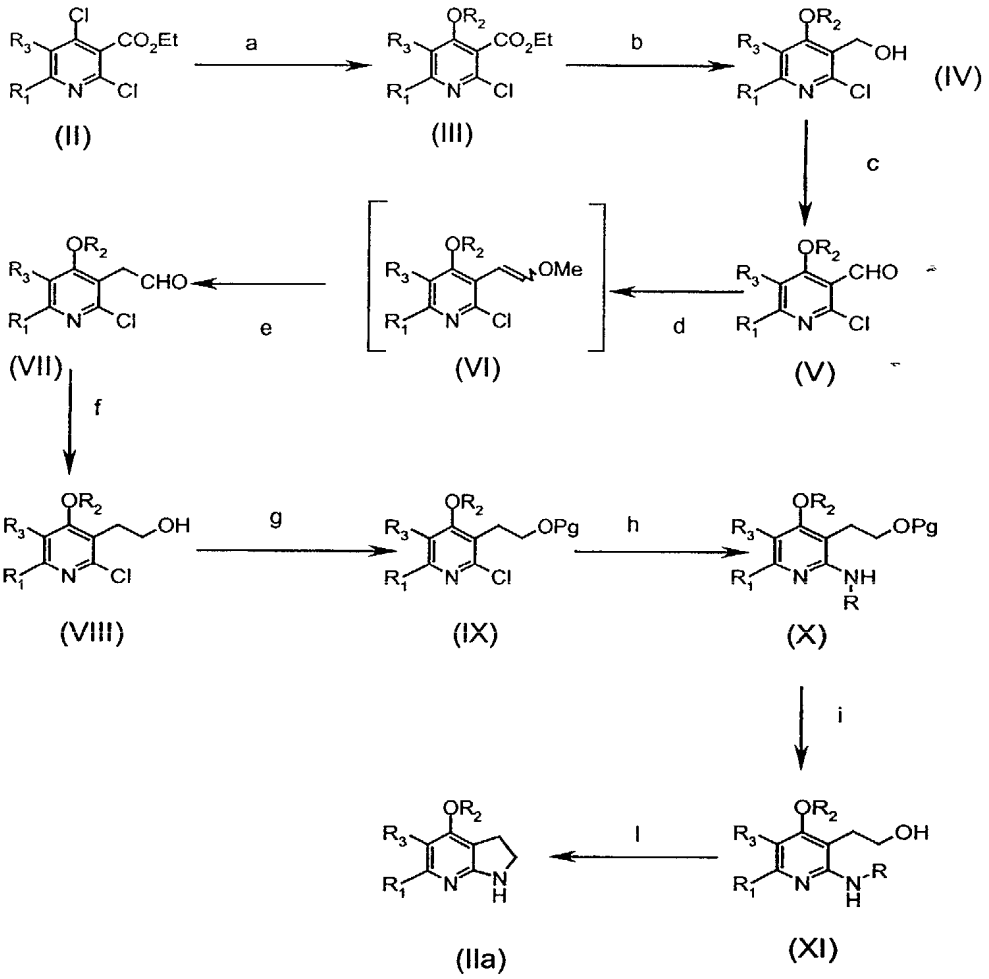
2-[4-(1-ethyl-propoxy)-6-methyl-2,3-dihydro-pyrrolo[2,3-*b*]pyridin-1-yl]-5-trifluoromethylbenzonitrile (1-5);
1-(2,4-dichloro-phenyl)-4-(1-isopropyl-2-methyl-propoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-6);
1-(2,4-dichloro-phenyl)-4-(1-isopropyl-3-methyl-butoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-7);
1-(2,4-dichloro-phenyl)-4-(2-methoxy-1-methoxymethyl-ethoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-8);
1-(2,4-dichloro-phenyl)-4-(2-ethyl-butoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-9);
1-(2,4-dichloro-phenyl)-4-(2-ethoxy-1-ethoxymethyl-ethoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-10);
1-(2,4-dichloro-phenyl)-4-(1-ethyl-methyl-allyloxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-11);
1-(2,4-dichloro-phenyl)-4-(1-methoxymethylpropoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-12);
1-(2,4-bis-trifluoromethyl-phenyl)-4-(1-methoxymethylpropoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]-pyridine (1-13);
1-(2,4-Bis-trifluoromethyl-phenyl)-5-(1-ethyl-propoxy)-7-methyl-1,2,3,4-tetrahydro-[1,8]naphthyridine (2-1).

In general, the compounds of structure (I) may be made according to the organic synthesis techniques known to those skilled in this field, as well as by the representative methods set forth in the Examples.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1, R_2, R_3, R_4, R_5, R_6, R_7 X and n have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (IIa), may be conveniently prepared starting from a compound of formula (II), according to the following Scheme 1:

Scheme 1



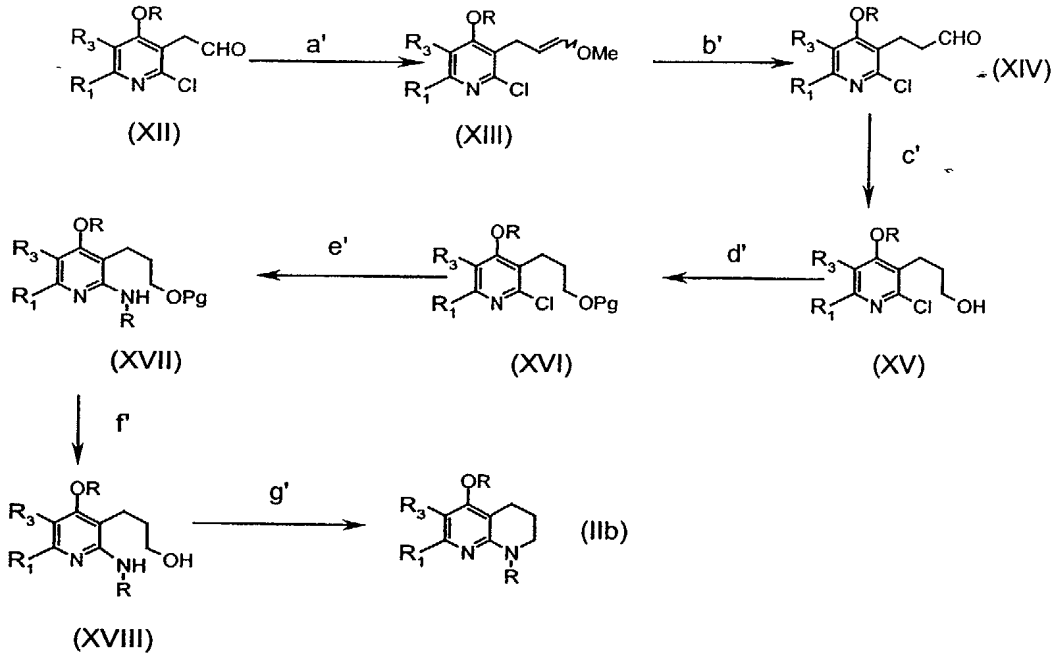
in which

step a	stands for conversion of chloride in the ether group of compounds (III), by reaction with the suitable R_2OH in basic conditions;
step b	stands for reduction of the ester group with a suitable reducing agent (such as DIBAl-H) to hydroxy group of compounds (IV);
step c	stands for oxidation of the hydroxy group with a suitable oxidising agent (such as Dess-Martin periodinane) to aldehyde group of compound (V);
step d	stands for formation of the aldehyde group of compounds (VII) by Wittig reaction in the usual conditions, followed by acid hydrolysis of the obtained enol ether (step e);
step f	stands for reduction of the aldehyde group with a suitable reducing agent (such as $NaBH_4$) to hydroxy group of compounds (VIII);
step g	stands for conversion of the hysdroxy group in the suitable protecting group of compounds (IX)(such as TBS: *tert*-butyldimethylsilyl);
step h	stands for Buchwald reaction by coupling with the suitable amine RNH_2;
step i	stands for deprotection reaction to give the hydroxy group of compounds (XI);
step l	stands for intramolecular cyclisation by heating after conversion of the hydroxy group of compounds (XI) in a suitable leaving group (such as

bromide, by reaction with CBr_4 and PPh_3) to give the final compounds (IIa).

Compounds of formula (IIb) may be conveniently prepared starting from a compound of formula (XII), according to the following Scheme 2:

Scheme 2



in which

step a'and b'	correspond to previous step d and e;
step c'	corresponds to previous step f;
step d'	corresponds to previous step g;
step e'	corresponds to previous step g;
step f'	corresponds to previous step i;
step g'	corresponds to previous step l to give final compounds (IIb).

Compounds (II) and (XII) may be prepared according to methods known in literature, like for example in Mittelbach, M.; *Synthesis*, 1988, 6, p.479-480.

Examples of suitable hydroxy protecting group include trihydrocarbyl silyl ethers such as the trimethylsilyl or t-butyldimethylsilyl ether. The hydroxyl protecting groups may be removed by well-known standard procedures (such as those described in Protective Groups in Organic Chemistry, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973)). For example when Pg is a t-butyldimethylsilyl group, this may be removed by treatment with triethylamine trihydrofluoride.

Pharmaceutical acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods. Thus the required enantiomer may be obtained from the racemic compound of formula (I) by use of chiral HPLC procedure.

The invention as herein described also includes isotopically-labeled compounds, which are identical to those falling within the scope of formulas I, Ia and Ib, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, iodine, and chlorine, such as ^{3}H, ^{11}C, ^{14}C, ^{18}F, ^{123}I and ^{125}I. Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. ^{11}C and ^{8}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site including CRF 1 and CRF 2 receptors and may be used in the treatment of conditions mediated by CRF or CRF receptors.

The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (J. Neuroscience 7: 88,1987) and Battaglia et al. (Synapse 1: 572,1987).

The CRF receptors-binding assay was performed by using the homogeneous technique of scintillation proximity (SPA). The ligand binds to recombinant membrane preparation

expressing the CRF receptors which in turn bind to wheat germ agglutinin coated SPA beads. In the Experimental Part will be disclosed the details of the experiments.

With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a Ki less than 10 μm.

Compounds of the invention are useful in the treatment of central nervous system disorders where CRF receptors are involved. In particular in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful for the treatment of dysfunction of appetite and food intake and in circumstances such as anorexia, anorexia nervosa and bulimia.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease (IBD) and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Compounds of the invention are of particular use in the treatment of gastrointestinal disorders such as irritable bowel syndrome (IBS); skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

Compounds of the invention are useful for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospam, hypoglycemia, hypoxia, anoxia, perinatal asphyxia cardiac arrest.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by CRF.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of condition mediated by CRF, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or a solvate thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.
Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium

hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or

intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Thus for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 300 mg e.g. 1 to 100 mg.

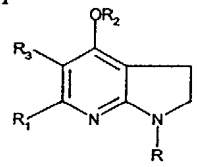
EXAMPLES

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refers to °C. Infrared spectra were measured on a FT-IR instrument. Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me_4Si, used as internal standard, and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m). Column chromathography was carried out over silica gel (Merck AG Darmstaadt, Germany). The following abbreviations are used in text: EtOAc = ethyl acetate, cHex = cyclohexane, CH_2Cl_2 = dichloromethane, Et_2O = dietyl ether, DMF = N,N'-dimethylformamide, DIPEA=N,N-diisopropylethylamine MeOH = methanol, Et_3N = triethylamine, TFA = trifluoroacetic acid, THF = tetrahydrofuran, DIBAl-H=diisobutylaluminium hydride, DMAP=dimethylaminopyridine, LHMDS= lithiumhexamethyldisilazane; Tlc refers to thin layer chromatography on silica plates, and dried refers to a solution dried over anhydrous sodium sulphate; r.t. (RT) refers to room temperature.

Example 1

Synthesis of representative compounds of structure (1a)



(1a)

Intermediate 1

2-Chloro-4-(1-ethyl-propoxy)-6-methyl-nicotinic acid ethyl ester

Dissolve 3-pentanol (3 eq) in anh. DMF at r.t., under N_2, and add NaH 80%/oil (3 eq). Stir the reaction mixture at 60°C for 20 min, or until gas evolution ceases. Add the 2,4-dichloro-6-methyl-nicotinic-acid ethyl ester (1 eq) and stir the reaction mixture at r.t. for 1.5 hr. Add water to destroy the excess NaH and pour the mixture in EtOAc/H_2O. Separate the phases and extract the aqueous layer with EtOAc (3x). Combine the organic extracts and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound obtained by flash chromatography to get the title compound.

Intermediate 2

[2-Chloro-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-methanol

Dissolve intermediate 1 (1 eq) in anh. CH_2Cl_2 at r.t., under N_2, and cool the solution to -78°C. Add diisobutylaluminium hydride 1.0M/cyclohexane (2 eq) and stir the reaction mixture at -78°C for 2 hr. Warm it up to 0°C and add a saturated solution of Rochelle's salt. Separate the phases and extract the aqueous layer with CH_2Cl_2 (2x). Combine the organic extracts and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to get the title compound.

Intermediate 3

2-Chloro-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-carbaldehyde

Dissolve intermediate 2 (1 eq) in anh. CH_2Cl_2, at r.t., under N2, and add Dess-Martin's periodane (1.12 eq). Stir the reaction mixture at r.t. for 60 min. Add a solution of $Na_2S_2O_3$ in sat. aq. $NaHCO_3$ and separate the phases. Extract the aqueous layer with CH_2Cl_2 (2x) and dry the combined organic extracts over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to get the title compound.

Intermediate 4

2-Chloro-4-(1-ethyl-propoxy)-3-(2-methoxy-vinyl)-6-methyl-pyridine

Add n-butyllithium 1.6M/hexanes (3 eq) to a cooled solution (0°C) of (methoxymethyl)triphenylphosphonium chloride (3 eq) in anh. THF under N_2. Stir the red reaction mixture at r.t. for 15 min. Slowly add a solution of intermediate 3 in anh. THF and stir the reaction mixture for an additional 30 min. Add water and EtOAc and separate the phases. Extract the aqueous layer with EtOAc(2x) and dry the combined organic extracts over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to get the title compound as a mixture of cis and trans isomers.

Intermediate 5

[2-Chloro-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-acetaldehyde

Add HCl 6N (2 volumes) to a solution of intermediate 4 (1 eq) in anh. THF (1 volume) at r.t.. Stir the reaction mixture at r.t. for 18 hr. Neutralize to pH 7 with solid $NaHCO_3$ and extract the aqueous solution with EtOAc (3x). Wash the combined organic extracts with sat. aq.

NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent to obtain the title compound which is used without further purification.

Intermediate 6

2-[2-Chloro-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-ethanol

Add $NaBH_4$ (1 eq) to a solution of intermediate 5 (1 eq) in anh. MeOH, at r.t., under N_2. Stir the reaction mixture at r.t. for 60 min. Add water and extract the aqueous solution with EtOAc (3x). Wash the combined organic extracts with sat.aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent to obtain the title compound, which is used without further purification.

Intermediate 7

3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2-chloro-4-(1-ethyl-propoxy)-6-methyl-pyridine

To a solution of intermediate 6 (1 eq) in anh. CH_2Cl_2, at r.t., under N_2, add 2,6-lutidine (2 eq) and tert-butyldimethylsilyl trifluoromethanesulfonate (5 eq). Stir the reaction mixture at r.t. for 18 hr. Add sat.aq. NH_4Cl and separate the phases. Extract the aqueous layer with EtOAc (3x) and dry the combined organic extracts over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

Intermediate 8

(2,4-Bis-trifluoromethyl-phenyl)-[3-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-4-(1-ethyl-propoxy)-6-methyl-pyridin-2-yl]-amine

To a solution of intermediate 7 (1 eq) in anh. DME, at r.t., under N_2, add $Pd_2(dba)_3$ (10 mol%), 2-(dicyclohexylphosphino)-2'-methylbiphenyl (30 mol%), K_3PO_4 (3 eq) and 2,4-bis(trifluoromethyl)aniline (2 eq). Place the reaction mixture in a microwave oven and irradiate for 20 min (100°C, 150 W, 60 psi). Add sat.aq. NH_4Cl and separate the phases. Extract the aqueous layer with EtOAc (3x), wash the combined organic extracts with sat.aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

Intermediate 9

2-[2-(2,4-Bis-trifluoromethyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-ethanol

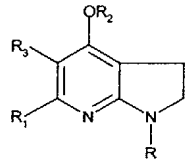
Add $Et_3N{\cdot}3HF$ (3 eq) to a solution of intermediate 8 (1 eq) in anh. THF, at r.t., under N_2. Stir the reaction mixture at r.t. for 3 hr. Add water and extract the aqueous solution with EtOAc (3x). Wash the combined organic extracts with sat.aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

Compound 1-1

1-(2,4-Bis-trifluoromethyl-phenyl)-4-(1-ethyl-propoxy)-6-methyl-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine;

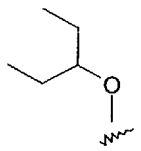
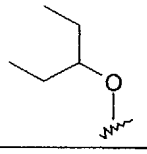
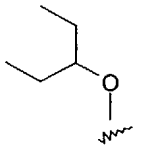
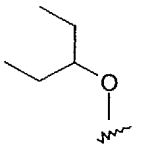
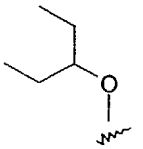
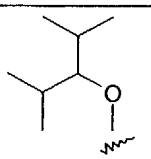
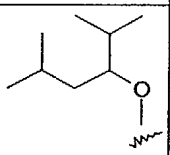
Add Ph_3P (2 eq) and CBr_4 (2 eq) to a solution of intermediate 9 (1 eq) in anh. 1,2-dichloroethane. Stir the reaction mixture at r.t.for 3 hr. Add sat.aq. $NaHCO_3$ and separate the phases. Extract the aqueous layer with EtOAc (3x), wash the combined organic extracts with sat.aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

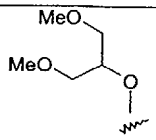
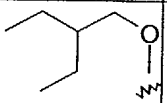
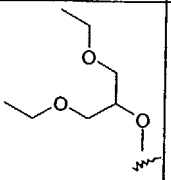
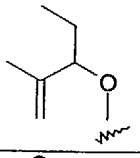
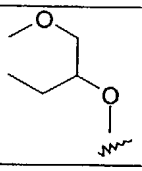
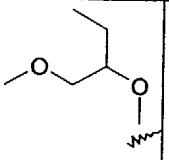
Further representative compounds of this invention can be prepared by the procedure set forth in the above examples.



(1a)

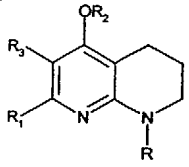
Table 1

Cpd. N°.	R	R_1	R_2-	R_3-
1-1	2,4-bis-trifluoro-methyl-phenyl	CH_3		H
1-2	2,4-dichlorophenyl	CH_3		H
1-3	2-trifluoromethyl-4-carboxyamino-phenyl	CH_3		H
1-4	3-(2-(1-ethyl-propoxy)-6-trifluoro-methyl)-pyridine	CH_3		H
1-5	2-cyano-4-trifluoro-methyl-phenyl	CH_3		H
1-6	2,4-dichlorophenyl	CH_3		H
1-7	2,4-dichlorophenyl	CH_3		H

1-8	2,4-dichlorophenyl	CH_3		H
1-9	2,4-dichlorophenyl	CH_3		H
1-10	2,4-dichlorophenyl	CH_3		H
1-11	2,4-dichlorophenyl	CH_3		H
1-12	2,4-dichlorophenyl	CH_3		H
1-13	2,4-bistrifluoro-methylphenyl	CH_3		H

Example 2

Synthesis of representative compounds of structure (1a)



(1a)

Intermediate 10

2-Chloro-4-(1-ethyl-propoxy)-3-(3-methoxy-allyl)-6-methyl-pyridine

Add *n*-butyllithium 1.6M/hexanes (3 eq) to a cooled solution (0°C) of (methoxymethyl)triphenylphosphonium chloride (3 eq) in anh. THF under N_2. Stir the red reaction mixture at r.t. for 15 min. Slowly add a solution of intermediate 5 in anh. THF and stir the reaction mixture for an additional 30 min. Add water and EtOAc and separate the phases. Extract the aqueous layer with EtOAc(2x) and dry the combined organic extracts over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to get the title compound as a mixture of *cis* and *trans* isomers.

Intermediate 11

3-[2-Chloro-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-propionaldehyde

Add HCl 6N (2 volumes) to a solution of intermediate 10 (1 eq) in anh. THF (1 volume) at r.t.. Stir the reaction mixture at r.t. for 18 hr. Neutralize to pH 7 with solid $NaHCO_3$ and extract the aqueous solution with EtOAc (3x). Wash the combined organic extracts with sat. aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent to obtain the title compound which is used without further purification.

Intermediate 12

3-[2-Chloro-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-propan-1-ol

Add $NaBH_4$ (1 eq) to a solution of intermediate 11 (1 eq) in anh. MeOH, at r.t., under N_2. Stir the reaction mixture at r.t. for 60 min. Add water and extract the aqueous solution with EtOAc (3x). Wash the combined organic extracts with sat.aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent to obtain the title compound which is used without further purification.

Intermediate 13

3-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-2-chloro-4-(1-ethyl-propoxy)-6-methyl-pyridine

To a solution of intermediate 12 (1 eq) in anh. CH_2Cl_2, at r.t., under N_2, add 2,6-lutidine (2 eq) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (5 eq). Stir the reaction mixture at r.t. for 18 hr. Add sat.aq. NH_4Cl and separate the phases. Extract the aqueous layer with EtOAc (3x) and dry the combined organic extracts over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

Intermediate 14

(2,4-Bis-trifluoromethyl-phenyl)-[3-[3-(*tert*-butyl-dimethyl-silanyloxy)-propyl]-4-(1-ethyl-propoxy)-6-methyl-pyridin-2-yl]-amine

To a solution of intermediate 13 (1 eq) in anh. DME, at r.t., under N_2, add $Pd_2(dba)_3$ (10 mol%), 2-(dicyclohexylphosphino)-2'-methylbiphenyl (30 mol%), K_3PO_4 (3 eq) and 2,4-bis(trifluoromethyl)aniline (2 eq). Place the reaction mixture in a microwave oven and irradiate for 20 min (100°C, 150 W, 60 psi). Add sat.aq. NH_4Cl and separate the phases. Extract the aqueous layer with EtOAc (3x), wash the combined organic extracts with sat.aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

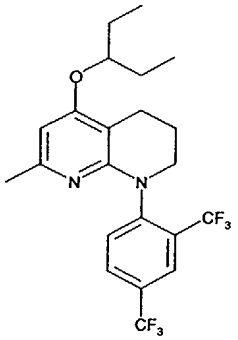
Intermediate 15

3-[2-(2,4-Bis-trifluoromethyl-phenylamino)-4-(1-ethyl-propoxy)-6-methyl-pyridin-3-yl]-propan-1-ol

Add $Et_3N{\cdot}3HF$ (3 eq) to a solution of intermediate 14 (1 eq) in anh. THF, at r.t., under N_2. Stir the reaction mixture at r.t. for 3 hr. Add water and extract the aqueous solution with EtOAc (3x). Wash the combined organic extracts with sat.aq. NaCl and dry over anh.

Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

Compound 2-1-
1-(2,4-Bis-trifluoromethyl-phenyl)-5-(1-ethyl-propoxy)-7-methyl-1,2,3,4-tetrahydro-[1,8]naphthyridine



Add Ph_3P (2 eq) and CBr_4 (2 eq) to a solution of intermediate 15 (1 eq) in anh. 1,2-dichloroethane. Stir the reaction mixture at r.t.for 3 hr. Add sat.aq. $NaHCO_3$ and separate the phases. Extract the aqueous layer with EtOAc (3x), wash the combined organic extracts with sat.aq. NaCl and dry over anh. Na_2SO_4. Filter the solids and evaporate the solvent. Purify the crude compound by flash chromatography (silica gel) to give the title compound.

Example 2
CRF Binding Activity

CRF binding affinity has been determined in vitro by the compounds' ability to displace ^{125}I-oCRF and ^{125}I-Sauvagine for CRF1 and CRF2 SPA, respectively, from recombinant human CRF receptors expressed in Chinese Hamster Ovary (CHO) cell membranes. For membrane preparation, CHO cells from confluent T-flasks were collected in SPA buffer (HEPES/KOH 50mM, EDTA 2mM; $MgCl_2$ 10mM, pH 7.4.) in 50mL centrifuge tubes, homogenized with a Polytron and centrifuged (50'000g for 5min at 4°C: Beckman centrifuge with JA20 rotor). The pellet was resuspended, homogenized and centrifuged as before.

The SPA experiment has been carried out in Optiplate by the addition of 100 µL the reagent mixture to 1µL of compound dilution (100% DMSO solution) per well. The assay mixture was prepared by mixing SPA buffer, WGA SPA beads (2.5 mg/mL), BSA (1 mg/mL) and membranes (50 and 5 µg of protein/mL for CRF1 and CRF2 respectively) and 50 pM of radioligand.

The plate was incubated overnight (>18 hrs) at room temperature and read with the Packard Topcount with a WGA-SPA ^{125}I counting protocol.

Example 3
CRF functional assay

Compounds of the invention were characterised in a functional assay for the determination of their inhibitory effect. Human CRF-CHO cells were stimulated with CRF and the receptor activation was evaluated by measuring the accumulation of cAMP.

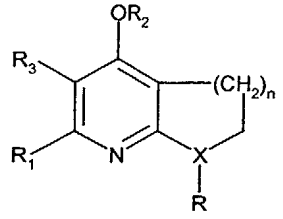
CHO cells from a confluent T-flask were resuspended with culture medium without G418 and dispensed in a 96-well plate, 25'000c/well, 100 µL/well and incubated overnight. After the incubation the medium was replaced with 100 µL of cAMP IBMX buffer warmed at 37°C (5mM KCl, 5mM $NaHCO_3$, 154mM NaCl, 5mM HEPES, 2.3mM $CaCl_2$, 1mM $MgCl_2$; 1g/L glucose, pH 7.4 additioned by 1mg/mL BSA and 1mM IBMX) and 1µL of antagonist dilution in neat DMSO. After 10 additional minutes of incubation at 37°C in a plate incubator without CO2, 1µL of agonist dilution in neat DMSO was added. As before, the plate was incubated for 10 minutes and then cAMP cellular content was measured by using the Amersham RPA 538 kit.

It is to be understood that the present invention covers all combinations of particular and preferred groups described herein above.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. Compounds of formula (I) including stereoisomers, prodrugs and pharmaceutically acceptable salts or solvates thereof



(I)

wherein

R is aryl or heteroaryl and each of the above groups R may be substituted by 1 to 4 groups selected from:
halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, $-COR_4$, nitro, $-NR_4R_5$ cyano, or a group R_6;

R_1 is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, halogen, NR_4R_5 or cyano;

R_2 corresponds to a group CHR_7R_8;

R_3 hydrogen, C1-C6 alkyl, halogen or halo C1-C6 alkyl;

R_4 is hydrogen, C1-C6 alkyl;

R_5 independently from R_4, has the same meanings;

R_6 is C3-C7 cycloalkyl, which may contain one or more double bonds; aryl; or a 5-6 membered heterocycle;
wherein each of the above groups R_6 may be substituted by one or more groups selected from: halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, C1-C6 mono or dialkylamino, nitro or cyano;

R_7 is hydrogen, C6-C6 alkenyl or C1-C6 alkyl, wherein each of the above groups R_7 may be substituted by one or more groups selected from: C1-C6 alkoxy and hydroxy;

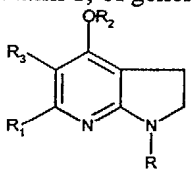
R_8 independently from R_7, has the same meanings;

X is carbon or nitrogen;

n is 1 or 2;

with the proviso that 5-(1-ethylpropoxy)-1,2,3,4-tetrahydro-7-methyl-1-(2,4,6-trimethylphenyl)-1,8-naphthyridine is not included.

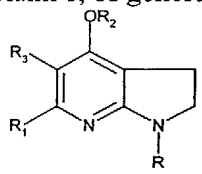
2. Compounds, according to claim 1, of general formula (Ia)



(Ia)

in which R, R_1, and R_2 are defined as in claim 1.

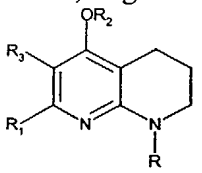
3. Compounds, according to claim 1, of general formula (IIa)



(IIa)

in which R, R_1, and R_2 are defined as in claim 1.

4. Compounds, according to claim 1, of general formula (IIa)



(IIa)

in which R, R_1, and R_2 are defined as in claim 1.

5. Compounds, according to any of claims from 1 to 4, wherein
R_1 is C1-C3 alkyl group or halo C1-C3 alkyl group and R_3 is hydrogen.

6. Compounds, according to any of claims from 1 to 5, wherein
R is an aryl group selected from: 2,4-dichlorophenyl, 2-chloro-4-methylphenyl, 2-chloro-4-trifluoromethyl, 2-chloro-4-methoxyphenyl, 2,4-dimethylphenyl, 2-methyl-4-methoxyphenyl, 2-methyl-4-chlorophenyl, 2-methyl-4-trifluoromethyl, 2,4-dimethoxy-phenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-chlorophenyl, 3-methoxy-4-chlorophenyl, 2,5-dimethoxy-4-chlorophenyl, 2-methoxy-4-isopropylphenyl, 2-methoxy-4-trifluoromethylphenyl, 2-methoxy-4-isopropylphenyl, 2-methoxy-4-methylphenyl, 2-trifluoromethyl-4-chlorophenyl, 2,4-trifluoromethylphenyl, 2-trifluoromethyl-4-methylphenyl, 2-trifluoromethyl-4-methoxyphenyl, 2-bromo-4-isopropylphenyl, 4-methyl-6-dimethylaminopyridin-3-yl, 3,5-dichloro-pyridin-2-yl, 2,6-bismethoxy-pyridin-3-yl and 3-chloro-5-tricloromethyl-pyridin-2-yl.

7. The use of a compound according to any of claims from 1 to 6, in the preparation of a medicament for use in the treatment of conditions mediated by CRF (corticotropin-releasing factor).

8. The use of a compound according to claim 8, in the preparation of a medicament for use in the treatment of depression and anxiety.

9. The use of a compound according to claim 8, in the preparation of a medicament for use in the treatment of IBS (irritable bowel disease) and IBD (inflammatory bowel disease).

10. A compound according to any of claims 1 to 6, for use in the treatment of conditions mediated by CRF (corticotropin-releasing factor).

11. A compound according to claim 10, for use in the treatment of depression and anxiety.

12. A compound according to claim 11, for use in the treatment of IBS (irritable bowel disease) and IBD (inflammatory bowel disease).

13. A pharmaceutical composition comprising a compound according to any of claims from 1 to 6, in admixture with one or more physiologically acceptable carriers or excipients.

14. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by CRF (corticotropin-releasing factor), comprising administration of an effective amount of a compound according to any of claims from 1 to 6.

15. A method, according to claim 14, in the treatment of depression and anxiety, comprising administration of an effective amount of a compound according to any of claims 1 to 6.

16. A method, according to claim 15, in the treatment of IBS (irritable bowel disease) and IBD (inflammatory bowel disease), comprising administration of an effective amount of a compound according to any of claims 1 to 6.

INVESTOR IN PEOPLE

Application No: GB 0216041.4 **Examiner:** Darren Handley
Claims searched: 1-16 **Date of search:** 13 December 2002

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance	
A	-	WO 98/08846 A1	(PFIZER) - see page 57, lines 7-8
A	-	EP 0527534 A1	(MERCK) - see claim 3

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[T]:

Worldwide search of patent documents classified in the following areas of the IPC[7]:

C07D, A61K

The following online and other databases have been used in the preparation of this search report :

Online: WPI, EPODOC, JAPIO, CAS-ONLINE